Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

4 The Vaccine Industry

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The vaccine industry is composed of companies that are engaged in any of the following activities: research (including that performed in industry and biotech), development, manufacture, or sales, marketing, and distribution of vaccines. They receive their revenue chiefly from sales of vaccine products or expectations thereof. The vaccine industry is relatively small, compared to the pharmaceutical industry, but growing. We estimate that total infectious disease vaccine sales in 2013 were more than $25 billion worldwide and expected to grow to about $35 billion by 2020. Although components of the vaccine industry are found in 50 countries worldwide, the large vaccine companies are primarily U.S.- or European-based and have the dominant share of vaccine business on a revenue basis; but regional companies are gradually growing their market share on a dose basis (Table 4.1).[1]

In the past 20 years, the vaccine business, a former laggard in the pharmaceutical business, has shown remarkable growth powered by new innovative vaccines coupled with superior pricing strategies (Fig. 4.1).[2] Specifically contributing to this spectacular growth were the varicella, hepatitis A, pneumococcal conjugate, shingles, rotavirus, meningococcal conjugate for A, C, Y, W, and human papillomavirus (HPV) vaccines, as well as myriad combination vaccines.

This projected growth may plateau in the early 2020s unless the vaccine industry continues to introduce new innovative products targeting diseases that impact the Western world. Sustaining this growth will be a challenge because of dwindling numbers of high-value vaccine targets for which the biology of protection is well understood (see Table 4.7).

The vaccine business is a capital-intensive business that requires considerable ongoing investment in manufacturing assets, facilities, and people to maintain compliance with ever-increasing regulatory directives. The recent departure of Baxter and Novartis from the vaccine industry is an ominous sign that reflects the continued financial pressure on the remaining four major vaccine makers. Further consolidation of this business is likely. In addition, new alliances will be formed between the big four manufacturers and emerging companies in India, China, and Brazil, to take advantage of increasing immunization rates in those countries as well as growth of their private markets.

The United States has been extraordinarily successful in vaccine research and development (R&D).[3,4] In the past 20 years, most new vaccines approved worldwide were developed in the United States. Approximately 15 new vaccines were approved in the United States between 1995 and 2014.[5,6] Since then, combinations of existing vaccines have been introduced for simplified pediatric vaccination resulting in a wider adoption of acellular pertussis vaccination. A polyvalent pneumococcal conjugate vaccine for infants introduced by Wyeth (now a subsidiary of Pfizer) has been widely adopted and has made Pfizer a major force in the vaccine business. Since 2006, several new vaccines have been licensed, including a combination of measles, mumps, and rubella (MMR) and varicella, as well as new vaccines against rotavirus, herpes zoster, HPV, meningococcus, influenza, and others. The HPV vaccines developed by Merck and GlaxoSmithKline significantly expanded the field of adolescent vaccines and confirmed market acceptance of premium pricing.

In the last 10 years, the vaccine industry in the United States and Europe has considerably improved its reliability as a supplier. Chronic shortages are a thing of the past; this turnaround has primarily been achieved by modernization of vaccine manufacturing and distribution infrastructure supported and funded by the profitability of the vaccine business. The Centers for Disease Control and Prevention (CDC) stockpiling of pediatric vaccines has alleviated some concerns of critical shortages in case of supply interruptions. But the industry's vulnerability because of dependence on single-sourced vaccines continues to be an unresolved concern. The regulators and the industry must proactively develop a solution to this critical challenge and avoid any future public health crisis resulting from vaccine shortages during a prolonged supply interruption.

VACCINE DEVELOPMENT

Vaccine development is difficult, complex, highly risky, and costly, and includes clinical development, process development, and assay development. The risk is high because most vaccine candidates fail in preclinical or early clinical development and less than 1 in 15 vaccine candidates entering Phase II achieves licensure. The high failure rate is the result of a variety of reasons:

1. Not fully understanding the biology of protection.
2. Lack of good animal models to predict vaccine behavior in humans.
3. Unpredictability of human immune system reactions to antigens as it relates to immunogenicity or safety.
4. The unpredictability of the impact of combining multiple components in a vaccine.

Vaccine development requires strong project management systems and controls and requisite skill sets among scientists and engineers. A key strategic document that guides the stakeholders in vaccine development is the "target product profile" (TPP). The TPP summarizes the desired characteristics and features of the product under development, the key attributes of the product that provide competitive advantage, and, finally, a topline roadmap of nonclinical and clinical studies required to evaluate the products efficacy and safety in the target population. A well-defined TPP provides all the stakeholders, including research, process development, manufacturing, clinical, regulatory, and senior management, with a clear statement of the desired outcome of the product development program.

Process development involves making preparations of the test vaccine that satisfy regulatory requirements for clinical testing including clinical lots, preclinical toxicology testing, and analytical assessment, and finally, scale-up methods that lead to a consistent manufacturing process at one-tenth of full scale. Usually three consecutive lots are tested in the clinic for immunogenicity. Assay development involves the definition of specific methods to test the purity of raw materials, stability and potency of the vaccine product, and immunologic and other criteria to predict vaccine efficacy. Go/no-go decisions must be made at each stage of clinical and process development and

must be data driven. Clinical, process, and assay development tasks must be closely integrated. Clinical development involves studies of the effects of vaccines on patients for safety, immunogenicity, and efficacy through a staged process: phase 1, early safety and immunogenicity in small numbers; phase 2, safety, dose ranging, and immunogenicity in 200 to 400 individuals; sometimes phase 2b, nonlicensure, proof-of-concept trials for efficacy; and phase 3, safety and efficacy trials that permit licensure, which generally require thousands of subjects.

"Process" can be broadly divided into two categories: bulk manufacturing and finishing operations. Bulk manufacturing includes cell culture and/or fermentation-based manufacturing followed by a variety of separation processes to purify the vaccine. The finishing operations include formulation with adjuvant/stabilizer followed by vial or syringe filling (including lyophilization in the case of live viral vaccines) followed by labeling, packaging, and controlled storage. Process development may be as costly as clinical development and is critically important to the overall success of a vaccine development program. As development proceeds toward licensure, costs escalate as clinical studies become larger, manufacturing scales up, and facilities must be built. Postlicensure studies of safety and efficacy (phase 4) of vaccines are essential and represent a large additional cost. It is important to note that, unlike pharmaceuticals, vaccines that pass early proof-of-concept studies in humans have a very high probability of achieving licensure.

Clinical activities are more visible than bioprocess development and clearly drive the go/no-go decisions that direct progress. The two are interwoven and each has rate-limiting steps, so they must be done in concert.

The first stage of vaccine development involves acceptance of a candidate from a basic research laboratory and development of a small-scale process and formulation to make material for Phase I study, analytical release assays, preclinical toxicology, immunological assays to evaluate clinical responses, an investigational new drug (IND) filing, and well-designed Phase I/IIa studies.

The second step is to complete the definition of product and process prior to initiation of Phase II dose-ranging studies, which may take a year or more. Product definition includes methods of synthesis/bioprocess steps, number of components, and stability/formulation. Stability, release, and raw material assays must be in place. Immunologic and other assays must be established to support dose-ranging studies, and a regulatory plan for vaccine process and product submissions must be written.

The third step is to define the clinical dose and arrive at the appropriate manufacturing scale, which may take 2 years or more. It results in the identification, manufacture, filling, and release of clinical-grade vaccine—usually in a pilot plant—demonstration of safety and a dose response in a Phase II clinical study; validation of critical assays to support Phase III clinical studies; consistency of lot manufacture (ability to produce three or more consecutive production-scale lots that meet all product specifications based on validated analytical methods); and completion of technology transfer to final site

TABLE 4.1 Market Shares of Vaccine Companies, 2014

Company	Year-End Earnings ($ Billion)[a]	Market Share (%)
GlaxoSmithKline	5.3	19.7
Merck & Co.[b]	6.2	23.4
Novartis	1.5	5.7
Pfizer	4.5	16.8
Sanofi[†]	5.8	21.9
Others	3.4	12.6
Total	**26.7**	**100**

[a]Company 2014 year-end earnings releases from EvaluatePharma (http://www.evaluategroup.com).
[b]Each includes 50% of revenues from Sanofi Pasteur MSD joint venture.

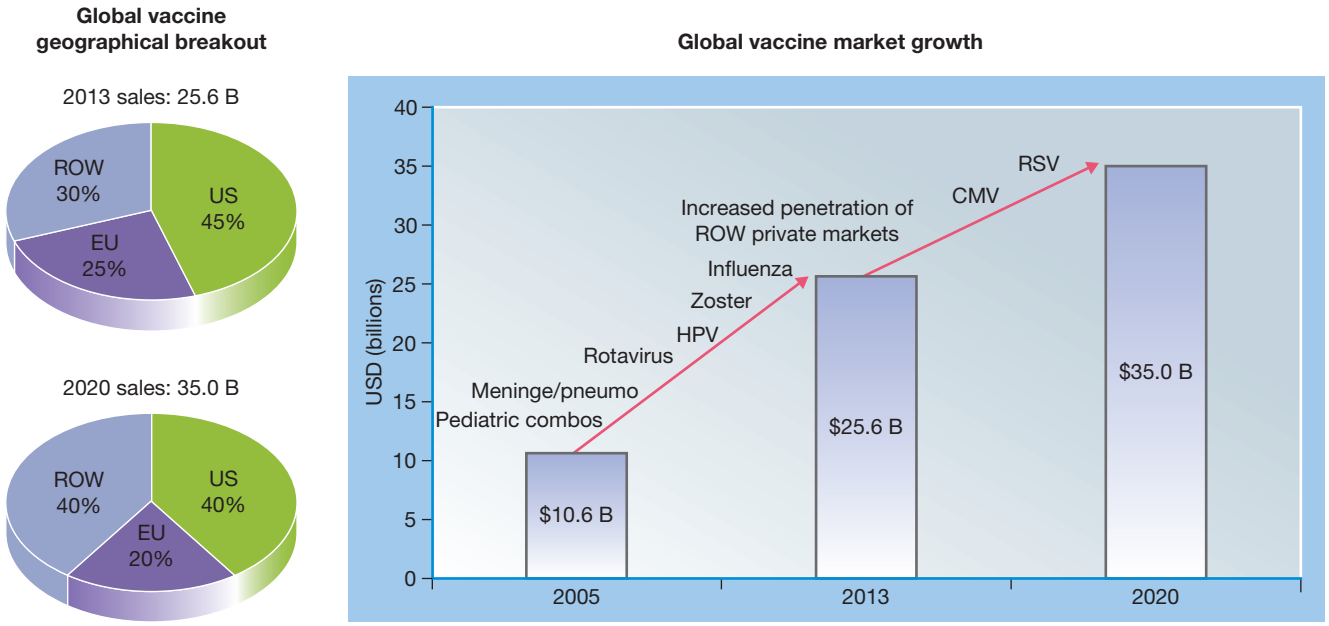

Figure 4.1. Global vaccine market growth. Worldwide projected vaccine business growth from 2005 to 2020. B, billion; EU, European Union; ROW, rest of world; US, United States; USD, U.S. dollars. *(Company earnings releases and presentations, EvaluatePharma research;* http://www.evaluategroup.com.*)*

of manufacture of full-scale lots, including process and analytical procedures. For vaccine targets for which animal studies are not predictive of efficacy in humans, such as HIV, malaria, and tuberculosis (TB), small Phase IIb proof-of-concept studies based on adaptive clinical trial designs may be used to gain confidence before committing significant resources for process development, analytic development, and factory construction.

In general, the analytical and release assays are particularly difficult to develop because, in most cases, vaccines are considered "not well-characterized" biologicals by regulatory agencies. The release assays initially involve functional potency assays such as animal immunogenicity prior to acceptance of more robust and precise in vitro assays that correlate with these functional potency assays. In general, variability of biological assays is a major hurdle in achieving process scale-up and manufacturing consistency.

The fourth stage is the completion of Phase III pivotal clinical studies and corresponding consistency lot studies, which requires 3 to 5 years. Keys to successful Phase III clinical studies are an accurate estimate of sample size based on disease incidence, low dropout rates, precise clinical end point definitions related to future label claims, and rigorous data management to the highest standards. In addition to clinical studies, scale-up and manufacture of consistency lots, including transfer to the facility of all assays, facility validation, demonstration of consistency and real-time stability are needed to support adequate shelf-life claims.

The final stage is Biologics License Application (BLA) preparation, licensure, and vaccine launch, which requires 1.5 to 2 years. Thus the total elapsed time for development is 10 to 15 years, assuming all activities proceed as planned.

Manufacturing plants are very expensive to construct, ranging from $50 million to $300 million depending on the size (dose requirements) and manufacturing complexity, with an additional expenditure of approximately 20% of that cost for cleaning and process validation activities that are now required under the current good manufacturing practices regulations. With few exceptions, each vaccine requires a different plant because of unique manufacturing requirements and the regulatory difficulties associated with changing over to a different product. Some processes are scalable, such as bacterial or yeast fermentation, so that increasing the size of the manufacturing unit (i.e., fermenter) will greatly increase the yield; unit cost will decrease with volume increase. Other manufacturing processes, for example, those dependent on viral growth in embryonated hen eggs or cell lines, are not scalable. Additional plants or modules within plants must be built to increase the throughput, so unit costs do not appreciably decrease with volume increases. Despite the complexity of bulk vaccine manufacturing, 3 to 5 years post–product launch, the fully burdened bulk cost of production for most of the older vaccines declines to as little as $0.50 to $1.00 per dose, and significant elements of product cost are primarily driven by activities related to filling, vialing, and packaging (Table 4.2). Established vaccines with a limited number of suppliers can generate very high profit margins over the product life cycle.

The commitment to build a plant must be made early (4 to 6 years before expected licensure) including a 6- to 12-month finished goods inventory build-up to expedite product to the market. Otherwise a gap of 1 to 5 years between licensure and product launch will occur.

Furthermore, it is far better to produce consistency lots in the final vaccine production factory to demonstrate the ability to manufacture the vaccine reliably and to use those lots in the Phase III efficacy trials. Otherwise, immune studies will be required for "bridging" the product used in the efficacy trial to material manufactured in the commercial factory. This is especially difficult if immune studies are not highly reproducible, as is the case with most cellular immune assays. Such decisions pose large financial risks if the product in development fails and requires access to large amounts of capital, an attribute usually restricted to large pharmaceutical companies.

TABLE 4.2 Vaccine Product Cost

	$/Dose
Bulk[a]	0.20–3.00
Fill/finish[b]	1.00–1.50
Syringe fill (optional)[c]	1.00–2.00
Total cost[d]	2.20–6.50

[a]Bulk range reflects older vaccines such as measles-mumps-rubella (MMR) and hepatitis B, at the low end, to newer vaccines such as shingles and live attenuated influenza at the high end.
[b]Fill/finish range reflects differences in speed, volume, and efficiency of operations.
[c]Syringe-filled product reflects cost of syringe and reduced line efficiency.
[d]Estimated fully burdened manufacturer's cost for U.S.-based operations in 2012.

TABLE 4.3 Vaccine Development Time Lines

Vaccines	Years to Approval
Varicella	25–30
FluMist	25–30
Human papillomavirus[a]	14–16
Rotavirus[a]	14–16
Pediatric combination vaccines	10–12

[a]From filing of first investigational new drug to approval.

Estimates of cost of development of a new drug or vaccine have risen from $231 million in 1991, to $802 million in 2003, to $1 billion in 2010.[7–9] These estimates take into account all costs, including R&D costs of products that fail, postlicensure clinical studies, and improvements in manufacturing processes. Approximately 50% of the cost is for construction; the remainder is the cost of capital interest. These numbers have been debated (others estimate $100 million to $200 million); however, the higher estimates have been validated in two ways. First, the number of new vaccines brought to licensure annually by a company or the industry is very small compared with other products, and correlates with R&D expenditures of $600 million to $800 million for each new product. Thus, if a company spends $100 million annually for vaccine R&D, one might expect one new product every 6 to 8 years, and this appears to hold true. Second, biotechnology companies that are focused on one vaccine and have successfully brought it to market have spent $500 million to $700 million on R&D as exemplified by the development of the live attenuated influenza vaccine by Aviron, now Medimmune. In summary, vaccine development from concept to licensure is a lengthy process as illustrated by timelines for some of the currently licensed vaccines (Table 4.3).

ROLE OF PARTNERS

To understand the predominant role of major pharmaceutical companies in the development of vaccines, one must examine the role of a vaccine development company in relation to its

TABLE 4.4 U.S. Network Partners' Relative Contributions to Vaccine Research and Development

	Research			Development		
	Basic/Related	Targeted	Process	Clinical	Manufacture	Postlicensure Studies
NIH	+++	+++	—	++	—	—
CDC	—	—	—	—	—	++
FDA	—	+	+	+	—	+
DOD	+	+	+	+	—	+
USAID	—	+	—	+	—	—
Large company	+	+++	+++	+++	+++	+++
Small company	+	+++	±	±	±	—
Academia	+++	+++		+++	—	—
NGOs (PDPs)	—	+	±	+++	±	—

CDC, Centers for Disease Control and Prevention; DOD, Department of Defense; FDA, U.S. Food and Drug Administration; NGO, nongovernmental organization; NIH, National Institutes of Health; PDP, product development partnerships; USAID, U.S. Agency for International Development.
Relative contribution: +++, major; ++, intermediate; +, minor; ±, varies by company.
Modified from Marcuse EK, Braiman J, Douglas RG, et al, for the National Vaccine Advisory Committee. United States vaccine research: A delicate fabric of political and private collaboration. Pediatrics. *1997;100:1015–1020.*

partners. The relative contributions of the various partners to the delicate fabric of vaccine R&D is shown in Table 4.4.[10] Several branches of the U.S. government play major roles in vaccine R&D.

The U.S. National Institutes of Health (NIH) is the major funding source via intramural and extramural (largely academic) programs of fundamental research (e.g., gene-based vaccines or T-cell memory studies) and directed research on pathogens (e.g., HIV), which may lead to new vaccine candidates. The NIH, through its vaccine trials network, has increased its role in clinical development domestically and internationally. In addition, the Dale and Betty Bumpers Vaccine Research Center at the NIH was established in 1999 primarily to pursue the development of HIV vaccines.

The Centers for Disease Control and Prevention (CDC) is the primary government agency responsible for epidemiological monitoring of disease trends. The CDC conducts disease surveillance and epidemiological studies to ascertain the prevalence and incidence of specific diseases; this information provides a rationale for prioritizing vaccine development. These studies by the CDC are performed in addition to studies conducted by the vaccine companies, such as Phase IV studies. Through the Advisory Committee on Immunization Practices (ACIP), the CDC recommends usage of vaccines, and is responsible for most of the public purchases (directly through the Vaccines for Children program for approximately 41%, and indirectly through other federal, state, and local government purchases for approximately 16%, together totaling approximately 57% of all childhood vaccines in the United States), thereby playing a major role in determining the demand and potential profit associated with vaccines. Professional organizations such as the American Academy of Pediatrics and the American Academy of Family Physicians also make recommendations for vaccine usage. There is no federal vaccine program for adults, although Medicare does reimburse for influenza and pneumococcal conjugate vaccines. Historically, many adults with private insurance were not covered for immunizations. However, the Affordable Care Act of 2010 requires health plans to cover vaccines recommended by the ACIP prior to September 2009 with no copayments or other cost-sharing requirements when those services are delivered by an in-network provider.

The Department of Defense (DOD) does targeted vaccine R&D to help it perform its mission of protecting deployable personnel and their families against infectious disease threats in the United States and abroad. Thus, the DOD assesses infectious disease risks in specific theaters and establishes prioritization of vaccine targets, especially those not being funded and developed in the private sector.

The U.S. Army Medical Research and Materiel Command (USAMRMC) is a major DOD organization conducting basic and applied medical research programs supporting military operations. The U.S. Army Medical Material Development Activity is its advanced product development agency, which aligns closely with the Walter Reed Army Institute of Research, the U.S. Army Medical Research Institute for Infectious Diseases, and the Naval Medical Research Center in conducting or supporting surveillance studies and vaccine trials. USAMRMC's longstanding overseas laboratories (e.g., in Thailand and Kenya) provide opportunities for the United States to partner with host nations in the development and evaluation of vaccines of shared interest. Some of the more recent efforts have focused on vaccines against malaria, dengue, HIV, norovirus, and Ebola. The Biomedical Advanced Research and Development Authority (BARDA) within the Health and Human Services Department was established in 2006 to facilitate development and purchase of vaccines and other products for public health emergencies. BARDA also manages Project Bioshield for the procurement of advanced medical countermeasures for biological as well as other threats and has successfully developed medical countermeasures against smallpox, anthrax, and botulinum toxin. In addition, BARDA is funding a variety of early stage novel vaccine approaches for pandemic influenza. BARDA essentially is intended to overlap with and close the gap between NIH-funded preclinical or initial Phase I trials and the more advanced Project Bioshield programs that are in late stage Phase III or licensure stages of development.

The U.S. Agency for International Development (USAID) supports limited R&D targeted toward those vaccines that potentially will have the greatest impact on children younger than age 5 years in developing countries. The Center for Biologics Evaluation and Research (CBER), a division of the U.S. Food and Drug Administration (FDA), is responsible for licensing new vaccines. CBER establishes standards for manufacturing processes, facilities, and pre- and postlicensing clinical studies to ensure that licensed vaccines are safe and effective (see Table 4.4). These standards have a profound

impact on the nature and direction of vaccine development and its costs. In addition, CBER maintains a strong research base internally, so it is better positioned to evaluate data from various studies. CBER remains the premier vaccine regulatory agency in the world.

Nongovernmental organizations (NGOs) are playing an increasing role in vaccine research. The Bill and Melinda Gates Foundation supports several organizations including the International AIDS Vaccine Initiative, the Malaria Vaccine Initiative, Aeras (dedicated to developing TB vaccines), and others with significant funding for development of vaccines that would have the greatest impact on diseases of developing countries. In addition, a related organization, Programs for Appropriate Technology in Health (PATH), is a nonprofit group that forges private sector partnerships to develop vaccine technologies suitable for the developing world. These product development partnership organizations (PDPs; essentially not-for-profit biotech companies) bring together specialized knowledge, animal models, immunologic assays, and field sites for vaccine testing as well as early capital investment to reduce the scientific technical risks, opportunity costs, and financial risk to their biotech and large pharma industrial partners. They also provide opportunities for validation of novel vaccine technologies and platforms.

The role of large, full-service vaccine companies (Table 4.5)[12] is predominantly in development. They engage

TABLE 4.5 Vaccine Companies Worldwide

FULL-SCALE COMPANIES WITH LARGE VACCINE FOCUS (~90% WORLD MARKET SHARE)	
France	Sanofi
United Kingdom	GlaxoSmithKline
United States	Merck Pfizer
OTHER FULL-SCALE COMPANIES WITH VACCINE DIVISION	
Australia	CSL (CSL Biotherapies)
United Kingdom	AstraZeneca (MedImmune)
United States	Johnson & Johnson (Crucell)
BIOTECH VACCINE COMPANIES	
Denmark	Bavarian Nordic
France	Vivalis
United States	Dynavax Emergent BioSolutions Genocea Novavax PharmAthene Protein Sciences Vical
REGIONAL COMPANIES	
Argentina	National Administration of Laboratories and Institutes of Health ANLIS Dr. Carlos G. Malbrán Sinergium Biotech S.A.
Bangladesh	Incepta Vaccine Ltd
Brazil	Ataulfo de Paiva Foundation Bio-Manguinhos–Institute of Technology on Immunobiologicals Butantan Institute Ezequiel Dias Foundation (FUNED)
Bulgaria	BB-NCIPD
Canada	InterVax Medicago
China	Beijing Minhai Biotechnology Co., Ltd Beijing Tiatan Biological Products Co., Ltd China National Biotec Group (CNBG) Hualan Biological Engineering Liaoning Cheng Da Biotechnology Co., Ltd (CDBIO) Sinovac Biotech Ltd. Walvax Biotechnology Co., Ltd Xiamen Innovax Biotech Co., Ltd
Cuba	Center for Genetic Engineering and Biotechnology Finlay Institute
Denmark	Statens Serum Institute
Egypt	The Holding Company for Biological Products & Vaccines (VACSERA)
India	Bharat Biotech International Ltd Biological E. Ltd Cadila Pharmaceuticals Ltd Hafkine Bio-Pharmaceutical Corporation Limited Indian Immunologicals Ltd Panacea Biotec Ltd Serum Institute of India Ltd
Indonesia	Bio Farma
Iran	Pasteur Institute of Iran Razi Vaccines
Israel	BiondVax
Italy	Okairos
Japan	Astellas Pharma Denka Seiken Japan BCG Kaketsuken Kitasato Institute Kyoto Biken Takeda
Korea	Boryung Biopharma Cheil Jedant (CJ Pharma) Dong Shin Pharma EuBiologics, Co., Ltd. Green Cross Corporation Korea Vaccine LG Life Sciences Ltd SK Chemicals
Malaysia	Pharm Malaysia
Mexico	Laboratorios de Biologicos y Reactivos de México, S.A. de C.V. (Birmex)
Netherlands	Netherlands Vaccine Institute
Poland	IBSS Biomed
Russia	Immunopreparat Research productive association, Ufa Products Immunologicals and Drugs, Irkustk RIVS, Saint Petersburg
Senegal	Torlak Institute of Immunology and Virology
Serbia	The Biovac Institute

Continued on following page

TABLE 4.5 Vaccine Companies Worldwide *(Continued)*

South Africa	BioNet Asia Co., Ltd
Thailand	The Government Pharmaceutical Organization Queen Saovabha Memorial Institute
Vietnam	Institute of Vaccines and Medical Biologicals (IVAC) The Company of Vaccine and Biological Production No. 1-VABIOTECH
CONTRACT MANUFACTURERS	
Germany	Boehringer Ingelheim IDT
Holland	DSM Biologics
Switzerland	Lonza Biologics
PRODUCT DEVELOPMENT PARTNERSHIPS	
Korea	International Vaccine Institute
United States	Aeras Global TB Vaccine Foundation Dengue Vaccine Initiative International AIDS Vaccine Initiative Malaria Vaccine Initiative Sabin Hookworm Vaccine Initiative

Data from World Health Organization. Influenza vaccine manufacturers. May 13, 2009. Available at http://www.who.int/csr/disease/influenza/Influenza_vaccine_manufacturers2009_05.pdf.

in some limited basic research and significant amounts of targeted research regarding specific organisms, but the preponderance of activity is in clinical and process development. Sufficient personnel and expertise in process development and chemical engineering reside almost exclusively in these companies; there is no other resource for such development. Clinical development that will satisfy FDA standards is also done mostly by the large companies, performed by academia and contract research organizations. Personnel and expertise in clinical research, regulatory affairs, data management, statistics, project management, and all other required disciplines also exist within the large companies. Perhaps most importantly, their management is structured to make rapid go/no-go decisions required to minimize risk and assess efficient vaccine development.

Many smaller organizations, often referred to as biotechnology companies, are engaged in vaccine research. They are often started by university scientists, supported by venture capitalists, and are capable of basic research on a vaccine idea. At this early stage, they usually have limited capacity in process development, manufacturing, and clinical development, and none in distribution, sales, or marketing. If research results are favorable, capacity in process engineering, clinical studies, and manufacturing must be enhanced or obtained by partnering. Because of the large cost of adding new capacities and expertise, many biotech companies in advanced product development will opt to partner with large, full-scale companies.

Although 60 or so small companies claim engagement in vaccine R&D, only about a dozen or so consider it a major activity, and only a very few, such as MedImmune, have made it to the market or close to the market on their own. More have licensed their products or technology platforms to larger companies that have then completed development, yielding new vaccines such as those for hepatitis B and *Haemophilus influenzae* type b. For example, the hepatitis B innovation came from the research laboratories of Chiron Corporation that succeeded in making hepatitis B surface antigen in yeast, and thus enabling Merck and GlaxoSmithKline to commercialize the modern hepatitis B vaccines. In the case of *H. influenzae* type b (Hib), Praxis Biologics and Connaught Laboratories pioneered the development of Hib polysaccharide and conjugate vaccines. These companies were eventually acquired by Sanofi and Wyeth-Lederle, respectively.

The greatest contributions of the biotechnology companies have been the introduction of multiple ideas into early vaccine development, and testing them to determine if they should be rejected or carried forward. These small companies are dependent on several factors for their success:

1. A vibrant basic research environment that allows for creation of new ideas, an environment that exists in well-funded (NIH) academic research programs.
2. A strong venture capital and investment community that views vaccine companies as potentially financially rewarding as other investment opportunities.
3. Strong patent laws providing the intellectual property protection that is essential for commercial success.

FUNDING SOURCES FOR VACCINE RESEARCH AND DEVELOPMENT

Funding sources for vaccine R&D include government, profits from sales of product, risk capital, and charitable foundations. The NIH competes with other federal agencies and programs for taxpayer support, and, in general, has been more successful than most. Similarly, vaccine R&D sponsored through the DOD, FDA, CDC, and USAID is competitive with other public needs as determined by the executive and legislative branches of government. Recent funding for bioterrorism vaccines (anthrax, smallpox) and emerging pathogens (Ebola, West Nile virus, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS], pandemic influenza) could have long-reaching impact on vaccine research and manufacturing and could potentially create new entrants into the vaccine business.

Risk capital from private investors is the primary source of funds for small companies. Investors are attracted to the potential profits of a new vaccine, a forecast determined in part by sales of current vaccines. Large vaccine companies, which are divisions of much larger pharmaceutical companies, seek a profit by selling products. On average, pharmaceutical companies reinvest approximately 18% of their profits from product sales into R&D, and this proportion applies to vaccine sales as well as other pharmaceutical products (Pharmaceutical Research Manufacturers Association, personal communication, 2001).

Because vaccine companies are subsidiaries of large companies, vaccine R&D and manufacturing must compete with other product areas for resources. Comparisons of the economics of the vaccine industry with the pharmaceutical industry in Europe, and separately in the United States, were performed by the Mercer Consulting Company in 1995 (Fig. 4.2).[13] These studies in the United States showed that the

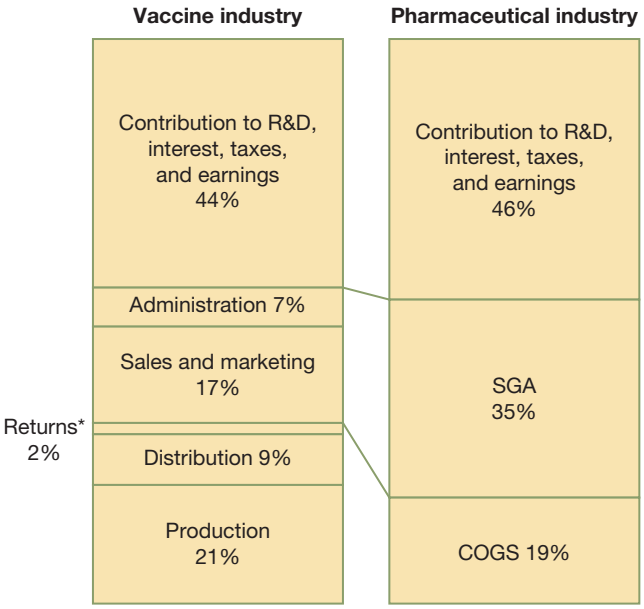

Figure 4.2. Major U.S. vaccine suppliers value-added chain (versus pharmaceutical industry averages). COGS, cost of goods sold; R&D, research and development; SGA, sales, general, and administrative costs. *Negligible returns (products that are sold and subsequently returned for a refund) in the pharma business. *(From Mercer Management Consulting Testimony on vaccine policy before the U.S. House of Representatives Committee on Commerce, June 15, 1995.)*

contributions to R&D, interest, taxes, and earnings after expenses were similar for the two industries (44% vs. 46%, respectively). However, the expenses were quite different. Significantly more was spent on production and distribution (32%, which includes production, distribution, and returns of product) in the vaccine industry compared with the pharmaceutical industry (19%), whereas the pharmaceutical industry spent more than the vaccine industry on sales, marketing, and administrative expenses (35% vs. 24%, respectively).

Consequently, within companies, there is an expectation that sales-to-expense ratios for vaccines will be similar to those of other pharmaceutical products, and that revenues will increase every year. Although some of this increase may be accomplished with sales volume, prices stabilize as vaccine products mature, and increased revenues are no longer possible; hence, the requirement for a steady rollout of new products. However, unlike pharmaceuticals, old vaccines continue to be profitable for a variety of reasons, including:

1. The absence of a regulatory pathway for generic vaccines deters potential entrants from engaging in a complex and expensive approval process.
2. In most cases, access to knowhow, such as proprietary cell lines, virus strains, and internally developed processes, is far more valuable than patent protection.
3. The birth cohort is renewable, providing an ongoing unmet need for vaccines.

As a result, sole-sourced vaccines, manufactured in fully depreciated assets, are profitable for pharmaceutical companies. One such example is the MMR vaccine, which after 40 years still has no competition in the United States. A typical vaccine company will have several vaccine candidates in early development, defined as all R&D through Phase I clinical testing (Table 4.6).[14-17] Those that are most promising in terms of technical feasibility, strong patent protection, and potential market size will be taken forward into development (post–Phase I). In addition, other candidate vaccines might be licensed from small companies. Even in the largest companies, only a few products can be in development at the same time. Thus, go/no-go decisions must be made and market size is a major determinant of the choice between two candidate vaccines, otherwise equal in technical feasibility and likelihood of success (Table 4.7).

This system works extremely well for vaccines with large potential markets in the developed world when technical feasibility is demonstrated. It does not work for vaccines for diseases that exist predominantly in the poorer regions of the world (e.g., TB); it works imperfectly for diseases of the developed world that affect relatively few persons because of geographic restriction (e.g., Lyme disease) or diseases limited to specific risk groups (e.g., cytomegalovirus [CMV] in transplant recipients), and it does not work when technical feasibility has not been demonstrated (e.g., HIV). The last problem has to be solved by a strong basic program in vaccine-related sciences, particularly for HIV, *Staphylococcus aureus*, malaria, and other challenging targets. Niche vaccines for developed-world markets are much more attractive to biotech than to large pharmaceutical companies as evidenced by recent biotech vaccine efforts for West Nile virus, Japanese encephalitis virus, the CMV-transplant indication, and dengue.

To involve large companies in development and manufacturing of vaccines to meet needs such as biodefense or health needs of poorer countries, incentives must be established to convince these companies that they should develop and manufacture such products. Such incentives might take the form of guaranteed purchase of certain volumes of a vaccine if specified standards are met, direct contracting by a government agency, or some other publicly funded mechanism.[18,19] The use of Advanced Market Commitments to create a funding mechanism for vaccines needed in the developing world has been endorsed by the G8 and pilot projects may be starting soon. This will not solve the problem of the high technical risk and opportunity costs associated with such vaccines, but it may contribute to the solution if combined with early investment. Companies may be willing to engage in such work. Indeed, they may already have donated or sold vaccines at very low prices to poorer countries. However, such practices alone will not solve the enormity of the health problems worldwide. Without special incentives, it is unrealistic to expect companies to engage in R&D on diseases that only, or predominantly, affect the poorer regions of the world.[13]

Manufacturers in developing countries (initially in India and China, and more recently in Brazil) are playing an increasing role in meeting these needs. Indeed, they already supply the majority of doses of older vaccines for such countries. As their expertise and capacity in vaccine R&D increases they will perhaps evolve into major participants in supplying new vaccines to the developing world. There are numerous manufacturers in these emerging countries, but a few truly stand out.

India

The vaccine industry has slowly mushroomed in India with several key companies emerging including Bharat Biotech, Biological E., Panacea Biotec, and others, but the largest one is the privately held Serum Institute of India. The Indian vaccine industry has significantly benefited from technology transfer from the West. Despite the industry's success, the available estimates suggest that R&D spending remains relatively low as a percentage of sales.[20]

Serum Institute of India is the world's largest producer of vaccines by number of doses, producing 1.3 billion doses

TABLE 4.6 Pipelines for Vaccine Development in Large, Full-Scale Companies

Sanofi	Merck	GlaxoSmithKline	Pfizer
Drugs or Indications in Phase I Trials			
Streptococcus pneumoniae	Dengue CMV	RSV	*Clostridium difficile*
HSV-2			
Rotavirus			
Drugs or Indications in Phase II Trials			
Rabies	Pneumoconjugate vaccine	*S. pneumoniae*	*Staphylococcus aureus*
Meningitis ACYW conjugate pediatric		Malaria	
TB		Nontypeable *Haemophilus influenzae* TB Hepatitis C	
Drugs or Indications in Phase III Trials			
Clostridium difficile	Ebola	MMR	Meningitis B
Dengue	Herpes zoster inactivated vaccine	Malaria Meningitis groups ACYW Ebola Zoster inactivated vaccine	

Data from company websites.
CMV, cytomegalovirus; HPV, human papillomavirus; HSV-2, herpes simplex virus type 2; RSV, respiratory syncytial virus; TB, tuberculosis.

TABLE 4.7 Vaccine Development Opportunities

Adenoviruses
Clostridium difficile
Chikungunya
Cholera
Cytomegalovirus (CMV)
Dengue
Ebola/Marburg
Enterotoxigenic *Escherichia coli*
Epstein-Barr virus
Herpes simplex viruses 1 and 2
HIV
Hookworm
Improved influenza
Leishmaniasis
Lyme disease
Malaria
Respiratory syncytial virus
Shigellosis
Staphylococcus aureus
Streptococcus A, B
Tuberculosis

a year; its products are used in more than 140 countries. Serum Institute is also one of the largest suppliers of measles-containing vaccines and the diphtheria-tetanus-pertussis (DTP) vaccines to U.N. agencies (UNICEF and Pan American Health Organization [PAHO]). The Institute makes its measles vaccine in MRC-5 cells instead of chick embryos and has productivity estimated at 10- to 20-fold higher than the measles vaccines made by Merck and GlaxoSmithKline. This privately held vaccine company has relentlessly invested in production facilities/infrastructure that surpasses some of the best biotech manufacturing facilities in the United States. So powerful has its growth been that one out of every two children immunized worldwide get at least one vaccine produced by the Serum Institute.

Vaccines recently developed by the Serum Institute are Nasovac (live attenuated trivalent influenza vaccine), MenAfriVac (meningococcal A conjugate vaccine), Pentavac (DTP Hepatitis B-Hib vaccine), and inactivated polio vaccine. The Institute continues to invest in R&D and is currently working on a rotavirus vaccine, a polyvalent meningococcal conjugate vaccine, a pneumococcal conjugate vaccine, and HPV Vaccine, combination vaccines containing acellular pertussis, and others.

China

China ranks as the world's largest vaccine consuming and manufacturing country, with an estimated annual output of 1 billion doses.[21] The original six government-owned regional biological institutes are now part of the China National Biotec Group (CNBG) consolidated under the China National Pharmaceutical Group Corporation (Sinopharm Group Co., Ltd.). CNBG has a large R&D center in Beijing that maximizes the synergies of the six affiliated institutions. Today, CNBG/Sinopharm supplies 85% of the doses of the 14 Chinese National Immunization Program vaccines. China's vaccine manufacturing capabilities are currently intensely focused on supplying their own domestic needs for the pediatric birth cohort of 17 million newborns annually. There are 46 registered vaccine manufacturers in China and 24 licensed vaccines. Several of the manufacturers are members of the Developing Countries Vaccine Manufacturers' Network (DCVMN). In 2013, the World Health Organization prequalified the Chinese-made Japanese encephalitis virus vaccine made by the Chengdu Institute for Biological Products in collaboration with PATH.[22] China became the first country ever

to approve a hepatitis E vaccine, which was developed by Xiamen Innovax Biotech.

Brazil

Brazil has four notable vaccine manufacturing companies. Bio-Manguinhos/Fiocruz is a government-owned entity that supplies the full demand for most vaccines under the Brazilian National Immunization Program (NIP). They also have a R&D collaboration with GlaxoSmithKline for a dengue vaccine. Butantan Institute is another government-owned institution that supplies the full demand for a smaller number of vaccines under the Brazilian NIP. Ataulfo de Paiva Foundation is nonprofit private institution that primarily supplies the BCG vaccine for the Brazilian market. Ezequiel Dias Foundation (FUNED) is a public institution and part of Minas Gerais state. Since 2009, it has supplied the meningococcal conjugate vaccine after transferring the technology from Novartis.

Summary

The Indian vaccine industry is the most advanced among these three developing countries, and is already providing a significant portion of the world's vaccine supply as well as developing new vaccines. China is on the verge of the transition from a domestic-only provider to a vaccine exporter, and is demonstrating solid progress in vaccine innovation. Brazil is approaching the point of supplying its own domestic needs, largely with technology transferred from the developed world. Together, these emerging players from middle-income countries will have increasing influence in the global vaccine industry during the coming years.

PRICING OF VACCINES

Pricing is a critical component of success for large companies and for venture funding of small companies since potential sales determine the desirability of an investment decision. The public expectation is for low vaccine prices, although this has changed somewhat in recent years with the introduction of several new, higher priced vaccines, such as varicella, rotavirus, pneumococcal conjugate vaccine, zoster vaccine, and HPV vaccine (Fig. 4.3). Large companies believe that vaccines should be priced according to value to society such as reduction in health care and related costs, relief from pain and suffering, and/or prevention of death, and that they should be rewarded for taking the enormous risks inherent in early vaccine development. Such prices far exceed manufacturing costs, but are essential to produce the revenue streams that allow vaccines to be competitive for R&D and manufacturing resources within large pharmaceutical companies or that make biotech companies attractive investment opportunities. In general, vaccine prices have declined when more than two companies have competed in a single vaccine market and profitability has fallen sharply. The influenza vaccine market highlights this cyclical ebb and flow of competitors, most recently with the H1N1 outbreak and shortages in 2009 leading to expanded competition and a vaccine surplus, followed by lower prices in 2010.

A vigorous large-company vaccine industry is dependent upon several factors:

1. A rich research environment sponsored largely by the NIH and mostly carried out in academia, as the source for new creative ideas.
2. Strong patent laws and protection of intellectual property.
3. Freedom to price products at fair levels related to value of product to society.
4. Well-implemented immunization practices.

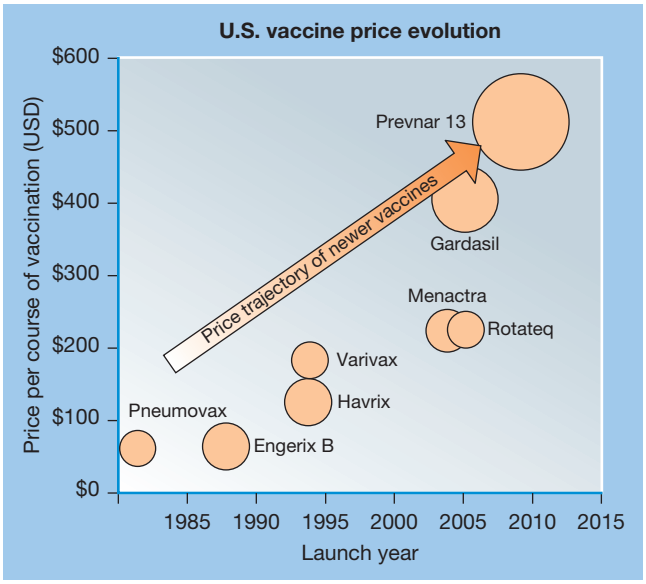

Figure 4.3. U.S. vaccine price evolution. Prices for vaccines are increasing relative to traditionally mandated products. USD, U.S. dollars. *(Data from U.S. CDC, IMS Knowledge Link, and NY Pharma Forum–Global Vaccines Outlook. Courtesy Kevin Fitzpatrick and Nitin Mohan of IMS.)*

Although the first two of these factors have been consistently present in recent years, downward pressure on price is a major threat to current companies and a disincentive to new companies. Freedom to price vaccines is restricted to the private market. Less than 50% of the vaccines for children sold in the United States are sold in the private market; the rest are sold to the federal or state governments at reduced prices. Controls are even greater in Western Europe and Japan, and internationally there is strong downward pressure on prices as one moves from well-developed to less-developed regions of the world.

In addition to the burden of partial price controls, the vaccine industry is subject to intense regulation. It cannot sell products until the vaccine and the facility in which it is manufactured are approved by the FDA or other regulatory authorities; each batch must be released by the appropriate regulatory agency; and the usage, and therefore market size, is largely determined in the United States by the CDC and in Europe by national regulatory authorities. Thus, the vaccine industry does not operate in a free-market environment, and its behavior reflects these constraints.

Vaccine business growth in the future will have three important drivers:

1. New vaccines for CMV, herpes simplex virus (HSV), respiratory syncytial virus (RSV), norovirus, *Clostridium difficile*, enterotoxigenic *Escherichia coli* (ETEC), "improved influenza," and others that will gradually shift the focal point of immunization activities from the pediatric sector to the adolescent and adult sectors.
2. Private market expansion in India and China driven by "high-income family" birth cohorts of 2 million and 6 million, respectively. This birth cohort roughly equals the combined birth cohort of 8 million in the United States and Europe. These high- and even middle-income individuals have shown the desire and ability to pay for vaccines at relatively high prices in relation to their incomes in these and other countries.

3. Public–private partnerships, or PDPs, on emerging pathogens such as pandemic flu, anthrax, SARS, botulism, Ebola, and others, will lead to large-scale manufacturing opportunities for these products. Toward the end of the 2020s, the PDPs for TB, malaria, and HIV are expected to produce effective vaccines for these diseases. A Boston Consulting Group study reports a surprising greater than $600 million per year market for a new TB vaccine (personal communication, 2012). Assuming such vaccines become reality, there is little doubt that the international donor community, working through organizations such as the Global Alliance for Vaccines and Immunization, will provide adequate funds for purchase of effective malaria, HIV, and TB vaccines, all of which are cost-effective, both in terms of cost per life saved and macroeconomic development of poor countries.

Vaccine Market

Estimates of the total worldwide vaccine market revenue are $25 billion. The top four Western suppliers (see Table 4.1) account for approximately 85% of these sales; the remainder comes from regional vaccine companies, the largest of which are located in middle-income countries such as India, China, and Brazil (see Table 4.5). The top four companies are slowly losing market share in doses to the DCVMN sourced doses and when polio eradication is achieved their dose share will drop to less than 20% of worldwide dose volume. In the coming years, as the eradication of polio becomes a reality, the developing country manufacturers will phase out their oral polio vaccine production. However, the need for inactivated polio vaccine will grow as developing countries adopt it into their pediatric immunization plans. As the demand for injected polio vaccine grows in developing countries, alternative approaches for local production will be explored, including access to bulk injected polio vaccine, tech transfer by big pharma as a part of their strategic alliances in developing markets, and potential introduction of alternative injected polio vaccine strains such as the Sabin strain. Another key driver will be the expansion of vaccine markets in India, China, and Brazil. Vaccine uptake rates in India, China and Brazil are still low compared with western countries (e.g., India's flu vaccine uptake in 2014 was 1.0 million doses vs. 140 million doses in the United States).[23,24] The immunization rates are also expected to increase in other low-income countries, which will increase vaccine dose requirements substantially. Most of this demand in low-income countries is expected to be met by manufacturers of DCVMN network. As the DCVMN expands its role, one would expect significant downward pressure on vaccine prices.

The delicate balance between innovation, government support, industrial expertise, and market forces has led to the establishment of a robust vaccine industry that will continue into the future. The industry is changing, however, with the growth of new markets in emerging economies and with the pressing need for new vaccines for the developing world. The current efforts of PDPs and public creation of markets in response to this need will be successful if lessons learned from the industrial vaccine effort are incorporated into these government and philanthropically driven expectations.

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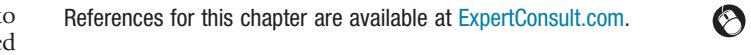

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